The most recent reports on this drug are based upon the experience of Major Walson of the Army, who treated 800 patients and gave more than 6000 injections. The method of treatment recommended by the board of medical officers of the Army and that method used by Walson is as follows:

An interval of seven days between each dose in each course of treatment. Treatment to consist of four courses of silver salvarsan and gray oil.

In the first course of treatment the first dose to be fifteen-hundredths (0.15) gm. of the drug. The second dose to be two-tenths (0.2) gm., and each of the remaining five doses of the course to be three-tenths (0.3) gm. of the drug.

At the end of the first course of treatment a Wassermann blood test is made, and then thirty days' rest.

In the second course of treatment three-tenths (0.3) gm. of the drug is given at each of seven injections, at seven day intervals, and is followed by two and one-half months' rest.

The third and fourth courses are the same as the second, with ninety days' interval between the two. Gray oil is used in conjunction with and at the same time as each injection of silver salvarsan, using eight-hundredths (0.08) gm., by intramuscular injection.

A blood Wassermann is recommended after each course, and a spinal fluid Wassermann after the second.—(Abstract from an editorial in the Journal of Laboratory and Clinical Medicine, June, 1921.)

INFANTILE PARALYSIS INCREASING

Doctor Hassler, of the San Francisco Health Department, has requested the Journal to call the attention of physicians to the increase of infantile paralysis. During the last two weeks ten cases have been reported in San Francisco, which is an increased rate over any year since the epidemic of 1917.

The Health Department considers it is safe to assume that a number of missed cases, or so-called abortive cases, exist for each developing paralysis that is reported.

With two or three months of climatic conditions favorable for the spread of this disease before us, there is danger of an epidemic of this disease, which we should not only foresee but forestall, if possible. This may be done with the assistance and co-operation of the medical profession.

There are abortive forms of the disease in which paralysis does not develop. These constitute the greatest menace in the spread of the infection, as these are the most difficult of diagnosis. The syndrome of fever, drowsiness, pain and sore throat, are very suspicious symptoms in children, and patients suffering from these symptoms should receive the special care of physicians at this time. The contact relations of sick children should be studied with special care.

The physician often is not aware of all these relations in the practice of other physicians. Therefore, prompt report to the Health Department will be of assistance to the physician and the public.

Early diagnosis and early report to the health offices is most important, and prophylactic precautions to prevent the spread of this disease should be practiced.

Infection is spread from person to person by secretions of the nose and throat of patients and carriers. It is claimed that dust and the stable fly carry the infection; therefore, all patients showing an otherwise unaccountable fever with drowsiness, pain and sore throat should be reported and the patient isolated in rooms screened against flies.

STREET VENDERS OF NOSTRUMS—The Board of Health of San Francisco, at a meeting held on July 21, 1921, passed the following resolution:

"Resolved, that the Board of Health place itself on record as being opposed to the issuance of licenses to anyone peddling medicines of any sort on the public streets, as such practice is a menace to public health; and, further, that the Health Officers be directed to refuse to issue permits for the vending of all medical nostrums and products on the public streets."

Original Articles

EPIDEMIC ENCEPHALITIS.*

By HERBERT C. MOFFITT, M. D., San Francisco.

Our interest in world-wide epidemics has been rudely awakened by the events of the last five years. In 1916, chiefly in New York and neighboring states, came a wave of poliomyelitis bringing with it at the crest unusual cases and high mortality. During 1917, culminating in the camps in winter and in the spring of 1918, respiratory infections succeeded each other in well marked periods or developed together during several weeks, possibly enhancing the virulence one of the other, and running clinical courses of severe and unusual types. Epidemic meningitis, pneumococcus and streptococcus infections were dangerous additions to the more usual camp scourges of mumps and measles. Later in 1918 rolled in the tidal wave of influenza from Europe, swamping the country in its initial strength and spreading rapidly from east to west. Possibly (as would appear from certain records in the Letterman Hospital) even before this wave reached us a smaller one, coming in the other direction and much modified by the long course across the Pacific, had broken on our shores. During the last three months of 1918 230,845 cases of influenza were reported in California, in 1919 82,682, in 1920 66,183 and a smaller wave is even now in the past month well raised above the average level of six months ago.

In 1917 and 1918 all these great infections were with us curiously pneumotropic although, starting about this time in central Europe, another infection with decided neurotropism was spreading gradually,. and gathering strength to break in the epidemic waves of 1918, 1919 and 1920; we are again witnessing the association of the "catarrhal" with the "nervous fevers" that has been noted in cycles through more than 400 years. Those particularly interested in various types of encephalitis and its epidemiology should read the interesting historical paper of Crookshank, the older articles of Leichtenstern, Oppenheim, Mauthner, Church, Comby and Longuet, as well as numberless papers, reviews and even monographs which have appeared since Von Economo's report of cases of lethargic encephalitis in Vienna in 1917.

Incidence: The incidence of the disease has undoubtedly everywhere been much underrated, many early cases being unrecognized or miscalled botulism, meningitis or influenza. Early in 1918 cases were reported in France and in March and April, 1918, in England; it seems probable that the "mysterious disease" of 1917 in Queensland and New South Wales reported by Cleland and Campbell should be classified with epidemic encephalitis, and the cases described by Breuil in Australia (Medical Journal Australia, March, 1918) clinically could be so grouped though pathologically nearer to poliomyelitis. The ultimate classification of the entity described by Bradford, Bashford and Wilson under the heading "Acute

* Read before the Fiftieth Annual Meeting of the Medical Society of the State of California, Coronado, May, 1921.

Infective Polyneuritis" is more doubtful. Five hundred and thirty-five cases were reported in England and Wales in 1919 and 202 cases in the first three months of 1920. Roger, from a survey in France, estimates that at least 10,000 cases occurred in 1920. To June, 1920, 3960 cases had been reported in Italy with 1013 deaths (25.6%). The first case in New York was reported September 4, 1918. In New York City 128 cases with 33 deaths were reported in 1919; 565 cases with 211 deaths in 1920; 61 cases in January and 195 in February, 1921. The U. S. Public Health Report of February 11, 1921, analyzes 222 of 225 cases reported in the United States between September 18, 1918, and May 19, 1919; 39 of these were excluded on account of faulty diagnosis; 46% of 122 cases had recently had influenza; no evidence of direct contagion was noted. It is plainly evident that statistical study of the disease except from carefully kept hospital or private records is of little value. No cases were reported in this state for 1918, 78 in 1919 and 76 in 1920. Up to April 1, 1921, the cases reported in the state at large number 170, in San Francisco 59. Many of my cases figure in these totals, others have not been reported because seen in consultation or in chronic stages of the disease.

Etiology: Loewe, Strauss and Hirschfeld of New York were the first to demonstrate that emulsions of the nervous system from fatal cases might transmit the disease to rabbits and monkeys. Their results have been confirmed by Thalhimer in this country, by Levaditi and Harvier in France, by Ottolenghi, D'Antona and Tonietti, Maggiore and Sindoni, Micheli in Italy. It has been fairly established by the same investigators that the virus is a filterable one, that it exists in the nasopharyngeal secretions, that it may be preserved for long periods in glycerin, that its virulence may be enhanced by rapid stepping-up through a series of rabbits, or may be decreased by drying, by treating with phenol or other chemicals. Harvier describes a certain fixed virulence after passage through several rabbits with symptoms occurring regularly in four to six days. On the other hand, Harvier and Levaditi have noted incubation periods of three or four weeks from material of chronic cases ending fatally after five or more months. Thalhimer has had rabbits survive for ten weeks after inoculation. Guinea pigs or mice may be used experimentally as well as rabbits. Infection occurs not only from intracranial injection of filtered emulsions, but from intraneural, intranasal, intraocular, intratesticular as well. Loewe and Strauss have emphasized the diagnostic value of injections of the filtered nasopharyngeal washings and of spinal fluid intracranially into rabbits. They have reported a minute filterable organism grown from the brain, nasopharynx, spinal fluid, and blood in man and from the brains of infected rabbits. Thalhimer has confirmed their results, but Levaditi and Harvier have been unable to do so.

The method of intracranial injection of spinal fluid or nasopharyngeal washings into rabbits as described by Loewe and Strauss is quite simple. In two of my cases material from the nasopharynx was used, in two others spinal fluid as well. In one case nasopharyngeal washings after filtration were injected into a monkey's brain by Dr. Carl Meyer. All the experiments were negative.

Surprisingly few instances of contagion have been demonstrated in man. Guillian and Lechelle cite one, Halle one, Claude and Laulerie two. No instances were observed in 122 cases analyzed by Smith. (Public Health Report February 11, 1921. 36:207.) Netter thinks that natural immunity must be high and that only individuals with substandard nervous systems are liable to be attacked. Lepine writes that in all of his fifty cases there were predisposing factors that might render the nervous system less restraint. Of my forty-eight cases, fifteen had had influenza in 1918 or 1919, two women had outspoken exopthalmic goitre; there was evidence of cerebrospinal syphilis in three men. Other histories of interest may be grouped as follows:

Unconscious from falls within a year, 2.
Repeated syncope, 1.
Familial tremor, 1.
Two attacks of facial paralysis, 1.
Previous chorea, 1.
Marked nervousness for years, 5.
Recent mental strain and surmenage, 3.

Fifteen of my cases were women, thirty-three men; the greater frequency of the disease in men has been recorded by a number of observers.

Pathology: A merchant of 34 had been nervous for years with frequent headaches, occasional pain in left arm, restless sleep with sudden sleep starts. Beginning January 31, 1919, he was ill three days in Chicago with cough, fever and mild delirium at night. He then returned home and was apparently well till February 22, when he felt feverish and sweated profusely. Headache then began and persisted in moderate intensity. February 26, occasional sharp pains began to shoot down the left arm like electric shocks and on the 28th intense burning pain became localized in the left index finger. This pain dominated his whole actions for the next two days, prevented rest, was not relieved by hypodermics of morphin, nothing could be found to explain it when suddenly it disappeared and was replaced by myoclonic jerkings of the left hand, arm, shoulder muscles. The patient became more restless and delirious, temperature was never over 99.6 degrees, reflexes were unmodified, eyegrounds unchanged, blood count normal, spinal fluid not under pressure with negative Wasserman, globulin slightly increased and 11 lymphocytes per cmm. March 4 myoclonus was persistent in the left arm and spread to the left abdominal and trunk muscles with hiccough due apparently to contraction of the left half of the diaphragm alone. Profuse sweating was seen on the left side of the face and neck without other evidence of sympathetic involvement. March 5 stupor replaced restlessness and delirium, respiration became irregular and the pulse, which had been from 90 to 96, rose to 120; death occurred suddenly early on March 6. No paralysis of eye muscles was noted at any time.

Autopsy by Dr. Rusk showed slight enlargement of the spleen and mesenteric glands. There were

no changes in the meninges or in cerebral arteries; there was no brain edema. Macroscopically sections of cerebral hemispheres, cortex, basal ganglia, pons, medulla and upper cord showed nothing abnormal. Microscopically there was typical perivascular lymphocytic infiltration scattered through basal ganglia and particularly marked in the brain stem. There were very few small hemorrhages. The cord was unfortunately not secured.

A woman, 35, entered the University Hospital April 23, 1919, with full-term pregnancy and complaining of pains and jerkings in both arms. She was delivered April 30 of a healthy child. Slight temperature followed delivery and was referred to thrombophlebitis of the left femoral vein. Mild delirium after a few days gave place to apathy and lethargy. May 10, ptosis, diplopia, masseter weakness, palsy of the right facial nerve were noted. There was a positive Babinski on the right. Spinal fluid showed a negative Wasserman, positive globulin, reduction of Fehling and 26 lymphocytes per cmm. Gradual improvement took place, apathy lessened, myoclonus ceased. Facial, masseter and eye muscle palsies disappeared, convalescence was apparently established when suddenly May 26 death occurred from pulmonary embolism.

Autopsy was done soon after death and showed the source of the pulmonary emboli to be in the deep leg veins. The brain superficially was normal, but the gray matter on section was pinker than normal. There were a few tiny hemorrhagic spots in the brain stem. Microscopically there were numerous small hemorrhages and numerous areas of marked lymphocytic infiltration along the small veins of basal ganglia, brain stem and pons.

August 29, 1920, a man 44 years of age was seen with Doctor Jacobs. When much overweight ten years ago he had had several attacks of syncope without obvious reason. Early in July sudden diplopia, due to paralysis of the right inferior rectus, came on without any other symptoms or signs. There was no history of syphilis and the blood Wasserman was negative, but specific treatment was given and the diplopia gradually got better. Ten intramuscular injections of mercury benzoate were given, followed August 19 by intravenous injection of neoarsphenamin .3, which was repeated August 26. Malaise and temperature of 101 degrees followed the last injection. On the 28th he was thoroughly examined by Doctors Shiels and Jacobs and nothing noted except slight diminution of the knee jerks. On the 29th at 3 p. m. he had pain in the right arm, followed at once by a chill and severe general convulsions; at 8 p. m. a second convulsion was succeeded by deep stupor. He was examined soon after and found to have no paralysis, no rigidity, knee jerks, Achilles rebexes were absent, but there was a positive Babinski on both sides. The eye grounds were negative, leucocytes 13,000, with normal differential. Spinal fluid was clear, not under pressure, contained no cells, gave a negative Wassermann and Lange and a positive Nonne and Naguchi. The urine, which had been normal on the 28th, contained on the 30th a large trace of albumen and numerous hyalin and granular casts. Coma persisted and death occurred on August 31. Autopsy by Dr. Ophuls showed the skull cap thick, heavy and congested, the dura normal, the piaarachnoid markedly congested. Numerous punctate hemorrhages dotted the cut surface of the brain sections, especially in the white substance. They were most numerous in the occipital lobes, corpus callosum and beneath the aqueduct of Sylvius and the fourth ventricle. Microscopical sections of various parts of the cortex showed extreme engorgement of the small veins and capillaries and a few small hemorrhages. The pia was not thickened. In sections of the corpus callosum and various parts of the brain stem there were many large perivascular hemorrhages, but no areas of round celled infiltration. As there was no positive evidence of syphilis in this case a clinical diagnosis of encephalitis was made, the possibility of arsphenamin encephalitis was raised but not considered probable. The autopsy findings were those of hemorrhagic rather than epidemic encephalitis. Careful systematic examination of the brain sections from the above cases will come later.

Marinesco, Wilson, Buzzard, Marie and Lhermitte, Bassoe, Wegeforth and Ayer have given excellent descriptions of the pathological changes. In general it may be stated that:

1. Lymphatic perivascular infiltration and small hemorrhages are the dominant lesions. The entire nervous system may be involved, but there is an undoubted predilection for the brain stem.
2. Piaarachnoid infiltration is less marked than in poliomyelitis or in general paralysis.
3. Destructive and degenerative parenchymatous changes are not nearly as extensive as in poliomyelitis. Extensive hemorrhages and large areas of softening are not usual, not nearly so common as in the hemorrhagic type of encephalitis that followed the influenza epidemic of 1889-90. And, yet as good observers as Mauthner and Leichtenstern could see no essential constant pathological differences between the so-called "influenzal" encephalitis and nona of that period.

The wide dissemination of the lesions in the nervous system, the rarity of extensive parenchymatous destruction, the shifting character of the vascular and perivascular changes, of ganglia degenerations and glia proliferation, the concentration of the virus at one time in one part of brain or cord and later in another will account for the variability of clinical pictures and the shifting scenes at various periods of the disease. In view of scattered reports that are appearing of autopsies on chronic cases it seems probable that the virus is capable of long viability and that fresh lesions may be excited in the region first attached or that entirely new areas may be invaded. Late symptoms are not necessarily the result of slowly progressing degenerations, therefore, but often the expression of a recrudescence of the disease. Von Economo followed one of his early cases eighteen

months, during which the clinical picture often changed. Death occurred after an acute exacerbation with marked dysphagia and autopsy showed old lesions in the brain stem with a recent involvement of the area about the glossopharyngeal nucleii. Archard and Foix, in describing the pathology of five cases, picture the manifest activity of a lesion found in a case of seven months' duration in which death occurred suddenly when the patient was apparently doing well.

Lesions outside the nervous system are rarely found at autopsy, which explains how little help the clinician can expect in diagnosis except from an analysis of the nervous symptoms. Two cases of Bassoe showed extensive petechiae in pleura, pericardium, bladder and stomach. Hemorrhagic blebs have been noted occasionally over heels, buttocks and backs, and bedsores as well. One of my patients finally died from septicemia resulting from excoriations of his skin from constant picking and scratching. Enlargement of the spleen is inconstant; swelling of the submaxillary and parotid glands has been described in a few instances.

Symptomatology: As is usual in world-wide epidemics, the first waves bring the most severe and the most typical cases. In the next years the clinical picture is less typical, or we learn to recognize more readily fruste forms that were overlooked at first. Unlike many infectious diseases the prodromal and general symptoms offer little help in diagnosis. The clinical charts of acute cases show no typical curves of temperature, pulse and respiration. As a rule there is slight temperature even in slowly developing cases. Hyperthermia I have seen only in cases with pontine localization or with terminal bronchopneumonia, but from other reports this is not always so. In a case fatal after twelve days' illness temperature never rose above 99.6. Pulse rates over 120 and very slow and irregular respiration, I have again only happened to see when pons and medulla nucleii were definitely involved. I have seen labial herpes three times, indefinite erythematous rashes on several occasions, but there are no characteristic skin changes; purpura and mucous membrane hemorrhages have been reported, but they must be extremely rare. The spleen has not been palpable in any of my cases. There are no cardiac lesions even in the pronounced choreiform types, and no pulmonary signs except in cases with terminal pneumonia. Netter and other French observers have noted enlargement of the salivary glands. Merklen has described an onset with arthritis and in one of Dr. P. K. Brown's observations pains in the joints followed soon on inaugural pains in the hands, arms and back. Claud has described swelling of tendon sheaths as well as joints. In Dunn and Heagey's analysis of 115 cases nosebleed was noted twice and I have seen it in one case. The essential lack of general symptoms in most cases is in strong contrast to other infections with early pronounced nervous symptoms—such as epidemic meningitis, tubercular meningitis, pneumonia, typhoid and is of great help in diagnosis. The patient looks too well, eats too well, has too clean a tongue, too low a temperature to have his delirium, stupor or many focal signs explained by one of the above diseases.

The most typical forms of epidemic encephalitis are slowly ushered in by indefinite malaise, moderate headache, constipation, a little fever and disturbance of vision, either blurring or distinct diplopia. At this stage there may be insomnia and decided restlessness with mild delirium or ephemeral disorientation either day or night. More characteristic is an increasing listlessness, lack of interest, apathy, asthenia which often deepens into the lethargy or stupor which has given its name to the disease. This mental indifference is accompanied with a striking loss of muscular tone and expression, or even more remarkable, with a decided increase of muscular tonus and rigidity. The masks of Parkinson or Hutchinson cover the former lively facial expression. Slow speech, some difficulty in swallowing occurs. In most severe cases the patient lies frozen in certain attitudes in bed and may say that he feels his body no longer belongs to him or obeys his will as before. In one young girl during this stage, speech was wholly inhibited, no voluntary movements, even chewing, could be executed and the extremities when placed in bizarre position would be held long by catatonic rigidity. Retention of urine is not unusual. Irregular coarse tremor and attacks of muscular jerking in face, trunk and extremities may occur. Twenty of my cases followed this course with characteristic symptoms developing so early in the disease that diagnosis did not long remain in doubt. In one young business man transient blurring of vision was the only symptom apart from lethargy that would overpower him during certain hours of the day so that he would fall asleep while dressing or while writing at his desk. In an active lumber merchant in perfect health dizziness and diplopia came suddenly during a motor trip and prevented his driving home. Nine of these patients, nearly all cases of 1919, recovered in from two to ten weeks and have remained well. A physician of 61, taken ill in October, 1919, is still weak and has difficulty with accommodation in reading. Two men are nearly well, but tire readily. One man with onset September, 1919, has still a persistent right internal rectus palsy. One woman of 63 with abrupt onset of external ophthalmoplegia and inactive pupils, lethargy and absent knee jerks, January, 1920, had fever for four weeks and gradually developed a Parkinson's syndrome more marked on the left. She slowly recovered, though always conscious that her left side was not as good as before and traveled to Seattle in summer. Three deaths in her family during September caused her great mental strain and in October there was a rapid return of lethargy, rigidity with again inactive pupils. Tremor and rigidity increased, lethargy persisted and she died February, 1921. A man of 36, in April, 1919, had pains, jerking and later weakness in the muscles of both thighs. In October, 1919, after peculiar paresthesiae in his abdomen he had diplopia, one week later lethargy and still later slow speech, stiffness of his extremities and gradually increasing difficulty in walking.

When examined in February, 1921, he presented the typical Parkinsonian mask, attitude and gait. His spinal fluid at this time was negative except for a Lange curve of 2233331000. Three other patients are even worse off with their legacies of tremor and rigidity. In the above group the chief determination of the virus must be in basal ganglia and brain stem. Mauthner in the encephalitis following the influenza epidemic of 1889-90 first suggested that the interruption of sensory impulses in the thalamus would account for the remarkable lethargy. As Bassoe observes, this lethargy must be regarded as a focal symptom, as it occurs in cases with few general symptoms and a perfectly free sensorium. The Parkinsonian and pseudobulbar syndromes probably represent localization in the corpus striatum and red nucleus.

It is hardly necessary to establish the eleven different clinical types set up by Tilnay and Howe or the fifteen or more listed by Archambault. The rigid adherence to classification may lead to overlooking important minor symptoms and fruste forms of the disease, though it has the great advantage of making us review our knowledge of the anatomy and physiology of the nervous system. In diagnosis it is often wise to forget schemes and remember general principles. We must remember that any part of the nervous system may be attacked by this disease, that peculiar combinations, progression and retrogression of symptoms may be observed, that modes of onset differ greatly, that certain unusual general or focal phenomena may dominate and confuse the picture. Certain difficulties of diagnosis and certain fruste forms will be sufficiently emphasized in the following without adherence to definite grouping:

1. The pain that often precedes myoclonus or other typical symptoms of the disease may be unusually severe, unusually localized and unusually persistent. In the fatal case recorded above intense burning pain was felt in the left index finger two days before myoclonic jerking began in the hand and arm. In a young woman of 25 pain in the left ear and side of the neck led to a diagnosis of ear disease. In a working man of 34 severe pains in both thighs came and went for several days before mild delirium and lethargy were noted. A youg man of 22 while at the theater began to have severe recurrent cramp-like belly pain which lasted for several days and was succeeded by pains down the legs with myoclonus. Denechau reported a case in which a decompression operation was done because of pain about the left ear, which was followed by Jacksonian epilepsy of the right arm. Bassoe mentions that in a young girl pain in the teeth sent her to the dentist; later the pain shifted to the left eye and ear. Intense visceral pain may occur as in the case of a man with such intense pain in the left testicle for two days, unrelieved by opiates, that he demanded operation. Massari (Wien. Klin. Woch. 33, p. 214, 1920) reports six interesting cases of hiccup, abdominal pain and myoclonus, one of which was operated upon for supposed abdominal disease. In one most remarkable case of mine the disease began abruptly with nausea, temperature of 103 and pain referred to the esophagus with a sense of coldness in the right hand; one week later intense pain was referred to the lower thoracic and upper abdominal regions, to be followed in two days by myoclonic jerks of the legs. Pain may be acute neuralgic or a persistent boring or burning or a disagreeable sense of coldness. In the young woman mentioned above with initial pain about the left ear and subsequent intense pain about the left ear and arms, with myoclonus in arms and trunk, burning sensations in the left shoulder and arm are still intensely annoying three months after the onset; there was an early dulling to temperature and pain perception with a burn from a hot water bag over the scapula. Sicard has described these persistent forms of radicular pains. In Pardee's article on the "Acute Descending Radicular Type" emphasis is laid upon the increase of pain as the process descends and the lumbosacral cord is reached. This has not held in all my cases; in one of which pain and myoclonus ascended from legs to trunk.

2. *Myoclonus* may be misinterpreted, though it should be a distinct help in diagnosis. Excellent descriptions of the so-called myoclonic type of the disease have been given by Bassoe, J. Ramsay Hunt, Tilney and Howe, Reilly, and many others. Nine of my cases showed marked myoclonic jerking at different periods of the disease—most often in early stages. In two others jerking of face and arm muscles was much less violent, more in small muscle bundles—myokymia rather than myoclonus. The jerking may begin in face, arm, leg or trunk muscles, and extraordinary movements and distortions occur. The association of rythmic jerking of abdominal muscles with hiccup has been noted above and we shall see later that hiccup lasting for days may precede the myoclonic type as well as other forms of the disease. It is to me impossible to explain why the severe initial radicular pain usually stops abruptly when myoclonic jerking begins.

3. *Convulsions* may abruptly open the scene, or, as in the case cited above, may follow some weeks after diplopia or other inaugural symptoms. A teacher of 59 had ptosis of the right lid appear abruptly March, 1920, masseter weakness, insomnia, jerking of the abdominal muscles followed in later weeks. In August, 1920, an epileptic convulsion occurred and seizures have been frequent ever since. A woman of 44 with unstable nervous system for years and recent family friction and insomnia had a general convulsion while lecturing October 11, 1919. This was succeeded by temperature of low grade, headache and in two weeks blurred vision, and a second convulsion. Hebetude, stupor, catatonia, mild delirium and hallucinations lasted until December. Spinal fluid November 15 showed globulin + +; 11 cells. Wassermann negative; December 2, globulin + 5 cells; Wassermann alcoholic antigen negative; cholesterin + +. Recovery took place gradually in January, 1921, under indifferent therapy. Cases with Jacksonian epilepsy have been reported by Raymond and Brissaud, Raymond and Claude, Sicard, Dumolard and Aubry.

4. *Meningeal symptoms* may dominate other clinical manifestations. A man of 35 with scars of old operations for tubercular glands of the neck was suddenly taken ill March, 1920, with vomiting, headache and retraction of the neck. Retraction of the neck, pains in the back, slight temperature, stupor persisted for three weeks. In the second week left hemiplegia gradually developed, lethargy continued and it was not until the end of May that he was well enough to leave hospital. Spinal fluid showed nothing abnormal. A boy of 17, who 10 months before had been knocked unconscious while boxing, had two weeks before entrance to the University Hospital blurring of vision, headache and vomiting. He was able to work, but was unusually dull and sleepy. Ten days later he was seized with severe headache, persistent vomiting and pain and stiffness of the neck. As he had a marked Kernig, head retraction, fever, variable reflexes, left external rectus palsy and signs of old tuberculosis in the right upper lobe, the suggestion of tubercular meningitis was strong. But he looked too well for a miningitis of this type causing so many symptoms and signs; the spinal fluid, though under pressure and containing 17 cells per cmm., reduced Fehling solution and showed no web. A history of early jerking in forearm muscles was obtained; his expression was apathetic and lethargic. Recovery was rapid and apparently aided by repeated spinal punctures which showed the effect of increasing irritation from the procedure in the rise of lymphocytes to 150 per cmm. Filtered nasopharyngeal washings and spinal fluid were injected intracranially into rabbits with negative result. In pre-epidemic days I should have called this a serous meningitis.

In the last two months I have seen three extraordinary cases which are most difficult to classify. A young married woman of nervous temperament, who had a long, exhausting illness two years ago following an abdominal operation, was in apparently good health when on March 12 she was suddenly seized with dizziness and intense pain in the back of the head and neck while writing letters at her desk. She was slightly irrational and had severe headache all night and next morning temperature of 99.2. By March 16 she was all right again. On the 18th there was return of severe headache with delirium and neck stiffness. Next day there was occasional peculiar disorientation for short periods, but March 22 she was well and up at dinner. March 23, while about to take a bath in the morning, she had a convulsion followed by delirium and severe headache. When seen she was extremely restless, with head retraction, no changes in reflexes or eye grounds, no obvious paralysis, though she complained of weakness and pains in the legs. On March 24, 10 c.c. of bloody spinal fluid was withdrawn with some temporary relief. The subsequent temperature is shown on the lantern slide. Meningeal irritative symptoms continued. March 30 right hemiplegia developed suddenly. Several spinal punctures showed old and fresh blood admixture. Culture from blood and spinal fluid were negative, Wassermann negative in both. Leucocytes were at first 15,200 and on April 1, 27,100 due to bronchopneumonia, which caused death April 5. No autopsy was obtained.

A female teacher, 31, was abruptly taken ill March 22, 1921, with violent occipital headache. Vomiting persisted for two days, head retraction was marked; delirium, stupor and diplopia were features of the first two days. Spinal fluid withdrawn March 25 and 26 by Dr. Downing of Berkeley, who kindly referred the patient to the University Hospital, was bloody both times, but otherwise negative. Leucocytes were at first 18000 with 83% polynuclears. On entrance to the hospital March 29 the picture was that of acute meningeal irritation. Spinal fluid March 30 gave the xanthocromia of old blood mixture; blood and spinal fluid cultures were negative. Although there was no positive evidence of meningococcus infection 15 c.c. of anti-meningococcic serum were given intraspinally without reaction. Rabbits inoculated with spinal and filtered nasapharyngeal washings did not develop encephalitis. The severe meningeal symptoms slowly began to improve early in April and by April 9 all things were better except that peculiar delusions and hallucinations kept recurring for short periods. April 10 there was renewed headache with vomiting, succeeded however, by several days of slow improvement. April 17 there was a severe relapse ushered in by headache, vomiting and head retraction. April 23, after complaint for two days of something wrong with the eyes, there was definite right ptosis and a wider pupil on the right. April 24 a convulsion was followed by complete right external and internal ophthalmoplegia, drooping of the right face, thickness of speech and some dysphagia. April 26 speech and swallowing were more impaired, the right patella jerk was increased over the left, respiration was slow and irregular with long pauses in which tremor of the face and hands would occur. The patient seemed moribund from advancing involvement of pons and medulla but again rallied, became conscious, the symptoms improved to some degree, and death did not occur until May 3, following another convulsion. The findings at autopsy are not yet clear, and further study will have to decide the cause of successive hemorrhages about the base of the brain with compression of the pons and medulla and involvement of the right oculomotor nerve. Fissinger and Janet, in addition to cases of military tuberculosis and sarcomatosis mistaken for epidemic encephalitis, report one instance of multiple meningeal hemorrhages with history much like the above. A woman of 40 (not syphilitic) was abruptly taken ill with headache, vomiting, diplopia, followed by unconsciousness. May 7, 1920, she was brought to hospital and found to have signs of meningitis; temperature 39, bilateral Babinski and bloody spinal fluid. From May 14 to 20 symptoms improved and temperature fell, May 22 relapse suddenly occurred with headache, diplopia, temperature 39 to 40, with fresh blood in the spinal fluid. Again improvement occurred, to be followed by a relapse of stupor, coma and

death June 7. Autopsy showed diffuse meningeal hemorrhage with preponderance on the right and no microscopical evidence of encephalitis. Inoculation experiments were negative. The cause of the hemorrhage was evidenly not determined.

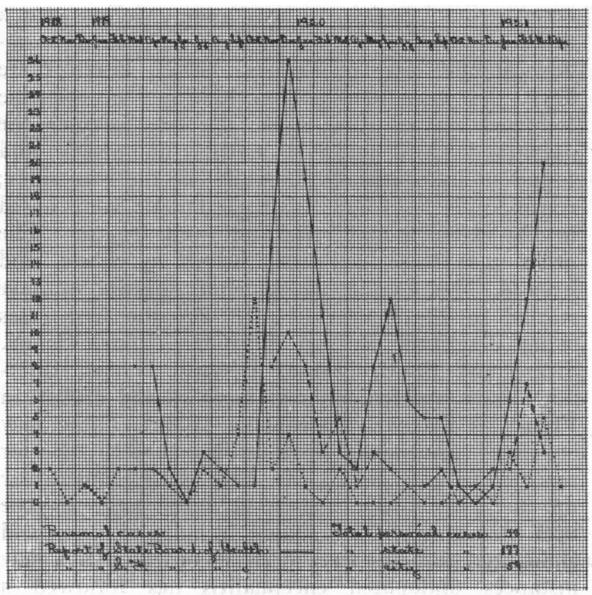
5. *Fruste Forms.* In the aftermath of all epidemics mild, atypical, peculiar cases begin to be recognized. Whereas in the rush of the epidemic many such cases are missed, there is danger later on that too many may be hastily accepted and other conditions overlooked. A man of 67 who had had influenza January, 1920, in January, 1921, felt feverish and out of sorts for a few days. He then had a tooth pulled after novocain injection, continued to feel somewhat below par and in a few days noticed his pupils much dilated and was unable to read. He consulted an oculist, who found absence of light and accommodation reactions and told him he had syphilis. Apart from arteriosclerosis and hypertension nothing was found except the pupillary changes, there being no evidence of syphilis and the pupils became normal after six weeks. A man of 56 had influenza November, 1918, followed by asthenia and diplopia in January, 1919; pupils reacted sluggishly to light and a diagnosis of cerebrospinal syphilis was made. When seen in March, 1919, pupils and eye muscles were normal and Wassermann reaction in blood and spinal fluid was negative. A man of 55 who had had in previous years two attacks of peripheral facial paralysis on different sides, in November, 1920, developed a complete right internal and external ophthalmoplegia. Apart from marked weakness and nervousness there were no other signs. Improvement started December 24 and recovery has since been complete.

I have notes of four cases of unusual vertigo coming on abruptly and associated with transient blurring of vision, with profound exhaustion for several weeks, in one case with apathy and lethargy for seven weeks. In two, Baranyi tests showed moderate involvement of the conduction paths. Three of these cases have wholly recovered and there seems no reason to suppose that they had relation to multiple sclerosis.

At this time particular hesitancy should be shown in making diagnoses of hysteria and neurasthenia and especial care taken to inquire for histories of diplopia, radicular pains with myoclonus, fever, mild delirium or periods of lethargy. An Italian girl was thought to be lazy and hysterical and punished by her parents until a Parkinsonian type of encephalitis sent her to the hospital. A young man had a sore throat and fever in September, 1919, and was left weak and nervous; he was thought to have "nervous prostration" until diplopia developed in a relapse two months later. Mild chronic recurrent types of the disease are particularly liable to misinterpretation, and it must be remembered that even after a year these may develop acute symptoms and end fatally.

6. *Epidemic Hiccup* is a most remarkable affection which has undoubted relations with epidemic encephalitis. In February, March and April, 1919, I saw five cases of hiccup, all in men, lasting from three to six days, and during this same period I heard of many more. Salinas, for a small community, seemed to have an unusual number; another case in October, 1919, lasted three days. No myoclonus accompanied and no sequelae followed any of these cases. In one instance the diaphragm was watched during an attack and found to be contracting equally on the two sides; considerable fluid and a big gas bubble were noted in the stomach and relief followed lavage. The other cases were apaprently helped by chloral and bromid. In Europe an epidemic appears to have started in the winter of 1919-20, the first cases being described by von Economo from Vienna. Sicard and Paraf, Dufour Bénard, Netter, Lhermitte have written entertainingly of the disease in France in the early months of 1920. There may be slight prodromes or a sudden onset. Netter reported a case lasting six days with temperature up to 39. Cases associated with pain in the neck and arm and myoclonic jerkings in arms and abdominal muscles have been recorded. In a few instances undoubted encephalitis has followed a period of hiccup. Clerc and Foix observed one case that started with hiccup, in forty-eight hours developed temperature up to 40, and died soon after in stupor. Autopsy showed inflammation of the entire spinal cord with lesions particularly marked about the third and fourth cervical segments. Von Economo mentions a fatal case with hemorrhages into the anterior and posterior horns of the cervical cord. Sicard reported three cases with hemiplegia; Cade and Dumollard two cases with meningeal irritation.

Diagnosis: The diagnosis in epidemic encephalitis depends chiefly upon the careful analysis, sifting and grouping of the varied nervous symptoms. The most important general symptom is fever. Ephemeral visual disturbances must be given considerable weight. It must be recognized that pupillary disturbances are by no means uncommon, and that isolated Argyle-Robertson pupils may occur. In my experience slight optic neuritis is not at all rare, but I have seen no marked cases, although a few have been reported. In four of my cases the question whether cerebrospinal syphilis could account for all the phenomena had to be weighed carefully, as there were signs which could be so interpreted, and once the Wassermann reaction was present in the blood and twice in the spinal fluid. Fever, however, was present in two cases, myoclonus in two cases, occupational delirium of a very characteristic type in one instance. Syphilis may have been a determinative factor, but in view of the quite typical combinations of symptoms and of the outcome there seems no reason to hesitate with the diagnosis of encephalitis. Guillain, Jacquet, Lechelle have particularly emphasized the identical symptomatology of certain cases of basal syphilis and the mesencephalic type of epidemic encephalitis. Fever and myoclonic jerking are important signs in favor of encephalitis. Lethargy and eye-muscle paralyses are not infrequent in brain tumors, especially in tumors of the quadrigeminal or pituitary regions. Differentiation from encephalitis may be difficult, but as a rule the symptomatology is less varied and less shifting, fever less often occurs, pressure



Cases of epidemic encephalitis in San Francisco and California

symptoms are more pronounced. Nonne has suggested that certain "pseudotumor complexes" may be due to encephalitis and Buzzard and Collier in England, Benechau and Blanc in France have described cases simulating brain tumor and characterized by marked intracranial pressure with choked disc and secondary optic atrophy.

In one case atrophy of trapezius, shoulder-girdle and upper arm muscles, in a second, atrophy of the shoulder and upper arm muscles alone was exactly that of poliomyelitis. One case has already been described as ushered in by pains in the neck and arms. The second case began with insomnia, mild delirium, blurring of vision, January 20, 1921. There was temperature 99 to 100, herpes and pulse rate of 120 for a week or more. Darting pains in the trunk were followed by jerking of the abdominal muscles and, after a month, by paralysis of the deltoids, trapezii, biceps, triceps and extensors of the wrist. When seen March 8, 1921, all muscles were rapidly recovering. I can look back on at least five indefinite cases seen in 1915 which could best be grouped under the heading polionecephalomyelitis. A man of forty-one began January 6, 1915, to have severe pain in the left great toe, which later extended into the foot. One week later he had sudden dysphagia and dysarthria, and, following this in a few days, great weakness of neck, shoulder and arm muscles, with slight weakness of the legs. About the same time he noticed blurred vision and ptosis. When seen six weeks after the onset there was considerable atrophy of the shoulder girdle, gluteii and quadriceps femoris muscles; reflexes were normal, Wassermann was negative. Recovery was slow, but complete. Retrospectively these cases might all now be classed as epidemic encephalitis.

Laboratory Tests: Blood and urine examinations are no help in diagnosis. There is usually a moderate leucocytosis, 7,000 to 15,000 leucocytes. The spinal fluid is usually not under increased pressure, though exceptionally it is decidedly so. It is nearly always clear, though a number of observers have described hemorrhagic fluid. There may be no increase in cells or counts up to 150 or more, practically all lymphocytes. Globulin is increased in over half the cases. Fehling solution is uniformly reduced (an important differentiation from tubercular meningitis). The Wassermann reaction is uniformly negative, except in complicating cerebrospinal syphilis. My experience with Lange's colloidal gold test parallels that of Davis and Kraus and Findlay and Shisken. There may be a perfectly negative curve, or, quite frequently, a moderate luetic, more rarely an outspoken paretic one.

Prognosis: The more cases one sees the more doubtful one becomes about authoritative assertions concerning prognosis. Even allowing for the fact that many cases are not reported, the immediate mortality of the disease is very high; the reports variously rate it from 20 to 40 or even 50 per cent. My cases number forty-two that I regard unquestioned, together with six fruste forms in which ophthalmoplegias, vertigo, slight myoclonus, lethargy, mild delirium occurred in such suggestive combinations that they in all probability should be classed with the disease. The cases of hiccup should be kept apart as representing much milder types of the infection (if they are to be classed here at all). All fruste forms have ended in practical recovery. The group of forty-two cases comprised twenty-nine men and thirteen women. Two women and five men died, seven in all—a mortality of 16 per cent—one woman who died suddenly over a month after onset of the disease from pulmonary embolism and not from encephalitis. An old man committed suicide by gas because incapacitated by the disease of over a year's standing. A man in a deplorable condition from the sequale of an intensely severe myoclonic type of the disease, which was observed for several weeks in the University Hospital, died eight months after the onset in Agnews from septicemia entering from excoriations. One woman died thirteen months after the onset from a relapse of the same type of the disease she had had at first. Others died from twelve days to seven weeks after the onset. A woman taken ill in April this year, is still in a critical condition. Six men and three women have been left more or less completely incapacitated by Parkinsonian tremor and rigidity. I do not take a hopeful view of the outlook in any of these cases; the danger of a recurrence is to be reckoned with at any stage. A child of five has been left in a remarkable hysteroid state with nocturnal delirium that, from the literature, is not an unusual sequel of the disease. Rutmeyer of Zurich reported eight cases of insomnia in children from five to eight, persisting three to six months after the disease; and Leahy and Sands (Jour. Am. Med. Ass., Feb. 5, 1921,) have recently written concerning the same condition; Hofstadt (Muench. Med. Woch., Nov., 1920,) gives a good description of most peculiar nocturnal actions in children from two and one-half to thirteen years which may precede or may follow en-

cephalitis. Eight patients have recovered with legacy of weakness, moderate vertigo, diplopia or slight blurring of vision. Five women and eight men send reports of complete recovery. It is interesting to speculate on how many relapses may occur even in this group; how often in the future we shall see cases of multiple sclerosis, Jacksonian or general epilepsy, localized serous meningitis with simulation of brain tumor, unusual tremors, etc., developing upon the basis of an encephalitis of the last years.

Treatment: There is yet no specific treatment. I feel that nervous tissues from rabbits killed by a fairly "fixed" virus should be prepared in a way similar to that adopted in the Pasteur treatment for rabies and used at least in the chronic recurrent types of the disease. Nothing decisive can be said in favor of hexamethylenamin. Arsphenamin has done no good in two cases of mine; Netter is of the opinion that it does definite harm. Tartar emetic intravenously has not been effective. Netter is still a strong advocate of the Fochier fixation abscess treatment; he cites twenty-five grave cases without treatment by this method, of which 50 per cent died. Out of twenty-seven equally grave cases, nineteen developed local abscesses after the injection of 1 cc. of turpentine, and all got well except a pregnant woman. Netter, like Dr. Margaret Schulze and others, have emphasized the gravity of prognosis in pregnancy. Serum from convalescent encephalitic or poliomyelitic cases has been given intraspinally without positive benefit. The experimental data of Levaditi and Harvier should counsel caution with this method of treatment. Autohemotherapy has been advocated by Mouriquand, Bourges and Marcaudier. Brill reported quick improvement in four out of five patients treated by injecting their own blood serum intraspinally after withdrawing 25-30 cc. of fluid. From my experience opium has not been as successful in controlling sleep and restlessness as chloral and bromid or paraldehyde. In three cases intravenous injection of 2.5 grains of calcium chlorid in 5 per cent solution seemed to have some influence in quieting persistent myoclonus. Hyoscin and scopolamin, hypodermically, will control tremor for a time, as in Parkinson's disease. Although we have learned much from the experiences of the last three years and, even before that, we had advanced far in the classification of infections of the brain and meninges beyond the knowledge of the first half of last century, I cannot help in closing to quote this paragraph on encephalitis from the interesting "Lectures on the Nervous System" of Marshall Hall: "Diseases *will not* suit themselves to our plans. Encephalitis, for example, is sometimes marked almost solely by violent delirium, and is then the *phrenitis* of nosologist; sometimes an early, if not the first symptom, is convulsion; sometimes there is violent headache as the chief symptom. In other cases, the disease is insidious in the highest degree; the patient seems *idle,* perhaps is suspected of *feigning;* he won't move or speak; and there may be *no* other marked symptom. Beware of these things. Cultivate an independent spirit of observation."

THE DIAGNOSIS OF HYPOTHYROIDISM*

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It is very probable that latent hypothyroidism will soon be considered a fairly common disease, although typical cretinism and myxœdema are rare. As a result of a recent study of modern diagnostic methods applicable to this condition, the writer has come to the conclusion that it is frequently possible to diagnose *myxœdema fruste* or Hertoghe's masked type of hypothyroidism where it is little suspected. The diagnosis is based upon the combination of certain clinical symptoms which can usually be regarded as merely indicative, together with the laboratory tests, particularly the basal metabolism. Thus in a small series of consecutive cases of thyroid disease which were analyzed and reported a year ago by the writer, two-thirds were found to be suffering from hypothyroidism, and in only three had the condition been previously diagnosed. As these cases are often greatly benefited and even cured by judicious thyroid treatment, the diagnosis of this condition becomes one of considerable importance. In the present paper, therefore, the clinical and laboratory data of diagnostic importance are collected together with a revision of the differential diagnosis in the light of advancing knowledge.

THE CLINICAL AIDS TO DIAGNOSIS

The family history is important. Questioning may bring out salient points such as history of early or uncontrollable obesity, goitres, protuberant eyes, tremor (thyrotoxicosis symptoms), stunted stature, hairlessness, defective nails, etc., as family characteristics. In doubtful cases in children, the parents should be examined on account of the strong familial tendency. In one instance, the diagnosis became evident in the cases of three children exhibiting retardation of growth through the discovery of marked dysthyroidism in the father.

In the history of the patient the following may prove of importance. In children, obesity, retardation of growth, backwardness at school, disinclination to play due to fatigueability; in adults, increase of weight unaccounted for by habits and diet, lassitude, forgetfulness, lack of vivacity, inability to carry out a vocation which previously was accomplished with ease, or a long history of indefinite ill-health. In adults and children marked predisposition to infections is suspicious in connection with other symptoms.

In considering the diagnosis of hypothyroidism, it is well always to bear in mind that every or any tissue or organ may suffer from a decreased or absent supply of the thyroid hormone. It becomes then particularly important to note the presence of various slight symptoms and signs occurring coincidentally in diverse situations. Among these may first be mentioned the body size in relation to age in the case of children, or to normal adult stature. The growth disturbance due to hypothyroidism sets in very early and is

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